Effect of maternal diabetes on fetal heart function on echocardiography: systematic review and meta-analysis

A. L. DEPLA[1#], L. DE WIT[1#], T. J. STEENHUIS[2], M. G. SLIEKER[2], D. N. VOORMOLEN[1], P. G. SCHEFFER[1], R. DE HEUS[1], B. B. VAN RIJN[3] and M. N. BEKKER[1]

[1]*Department of Obstetrics and Gynaecology, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands;* [2]*Department of Pediatric Cardiology, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands;* [3]*Department of Obstetrics and Fetal Medicine, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands*

CONTRIBUTION

What are the novel findings of this work?
Echocardiographic evaluation of fetal heart function shows that maternal diabetes is associated with functional impairment, not only in pregestational but also in gestational diabetes. The results of a meta-analysis of multiple functional sonographic markers support these findings.

What are the clinical implications of this work?
Current routine evaluation of structural heart abnormalities may not be sufficient to comprehend fully the effects of maternal diabetes on fetal cardiac development and function. Functional impairment detected by ultrasound should be further evaluated in relation to immediate perinatal outcome and long-term offspring cardiovascular health.

ABSTRACT

Objective *Maternal diabetes in pregnancy is associated with structural anomalies of the fetal heart, as well as hypertrophy and functional impairment. This systematic review and meta-analysis aimed to estimate the effect of maternal diabetes on fetal cardiac function as measured by prenatal echocardiography.*

Methods *We performed a search of the EMBASE, PubMed and The Cochrane Library databases, from inception to 4 July 2019, for studies evaluating fetal cardiac function using echocardiography in pregnancies affected by diabetes compared with uncomplicated pregnancies. Outcome measures were cardiac hypertrophy and diastolic, systolic and overall cardiac function as* assessed by various ultrasound parameters. The quality of the studies was assessed using the Newcastle–Ottawa Scale. Data on interventricular septal (IVS) thickness, myocardial performance index (MPI) and E/A ratio were pooled for the meta-analysis using random-effects models. For pregnancies with diabetes, results were reported overall and according to whether diabetes was pregestational (PDM) or gestational (GDM). Results were also stratified according to the trimester in which fetal cardiac assessment was performed.*

Results *Thirty-nine studies were included, comprising data for 2276 controls and 1925 women with pregnancy affected by diabetes mellitus (DM). Of these, 1120 had GDM, 671 had PDM and in 134 cases diabetes type was not specified. Fetal cardiac hypertrophy was more prevalent in diabetic pregnancies than in non-diabetic controls in 21/26 studies, and impaired diastolic function was observed in diabetic pregnancies in 22/28 studies. The association between DM and systolic function was inconsistent, with 10/25 studies reporting no difference between cases and controls, although more recent studies measuring cardiac deformation, i.e. strain, did show decreased systolic function in diabetic pregnancies. Of the studies measuring overall fetal cardiac function, the majority (14/21) found significant impairment in diabetic pregnancies. Results were similar when stratified according to GDM or PDM. These effects were already present in the first trimester, but were most profound in the third trimester. Meta-analysis of studies performed in the third trimester showed, compared with controls, increased IVS thickness in both PDM (mean difference, 0.75 mm (95% CI, 0.56–0.94 mm)) and GDM*

SYSTEMATIC REVIEW

(mean difference, 0.65 mm (95% CI, 0.39–0.91 mm)) pregnancies, decreased E/A ratio in PDM pregnancies (mean difference, −0.09 (95% CI, −0.15 to −0.03)), no difference in E/A ratio in GDM pregnancies (mean difference, −0.01 (95% CI, −0.02 to 0.01)) and no difference in MPI in either PDM (mean difference, 0.04 (95% CI, −0.01 to 0.09)) or GDM (mean difference, 0.03 (95% CI, −0.01 to 0.06)) pregnancies.

Conclusions *The findings of this review show that maternal diabetes is associated with fetal cardiac hypertrophy, diastolic dysfunction and overall impaired myocardial performance on prenatal ultrasound, irrespective of whether diabetes is pregestational or gestational. Further studies are needed to demonstrate the relationship with long-term outcomes. © 2020 The Authors. Ultrasound in Obstetrics & Gynecology published by John Wiley & Sons Ltd on behalf of International Society of Ultrasound in Obstetrics and Gynecology.*

INTRODUCTION

Worldwide, the prevalence of diabetes mellitus is rising, both in the general population and in pregnant women[1,2]. The obesity epidemic, the trend towards higher maternal age, and a general decrease in physical activity all contribute to the rising prevalence of both gestational diabetes mellitus (GDM) and pregestational diabetes mellitus (PDM)[3]. Recent estimates are that GDM affects up to 9–25% of pregnancies, closely following the incidence of diabetes and obesity in the general population[4]. Over 21 million live births were estimated to have been affected by some form of hyperglycemia in pregnancy in 2017[2].

Pre-existing diabetes in pregnancy is associated with increased risks for congenital anomalies of the heart, including septal defects, transposition of the great arteries and persistent truncus arteriosus[5–7]. In addition, morphological changes, such as cardiac hypertrophy, have been observed following fetal exposure to elevated glucose levels in PDM as well as in GDM[8]. Besides structural and morphological changes, maternal diabetes can result in sonographic changes in the fetal heart that are suggestive of functional impairment[9]. These functional changes include elevated heart rate, impaired ventricular filling and obstructed outflow tract, leading to systolic and diastolic dysfunction and decreased overall myocardial performance[9–11]. Impaired fetal cardiac function is associated with adverse pregnancy outcome and neonatal morbidity[12,13]. Moreover, although cardiac hypertrophy usually resolves spontaneously postpartum, there is growing concern that *in-utero* and early-life cardiac dysfunction may persist, and may potentially have long-lasting effects, predisposing to future cardiovascular disease[9,14,15].

Given the clear risk for structural cardiac malformations, routine clinical practice includes an advanced fetal ultrasound scan in pregnancies with PDM, which encompasses detailed cardiac evaluation[16]. However, current practice does not include evaluation of fetal cardiac function during the course of pregnancy, since the prevalence, type and impact of functional changes on echocardiography are still unclear. With the growing burden of maternal diabetes, both pregestational and gestational, and evidence that the impact goes beyond structural abnormalities, more insight into the effects of maternal diabetes on fetal heart development and function is essential.

The aim of this systematic review and meta-analysis was to provide a detailed overview of the effects of maternal diabetes, both GDM and PDM, on fetal cardiac function assessed prenatally by ultrasound.

METHODS

We followed the statement on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses[17].

Data sources and searches

Systematic literature searches were conducted in PubMed, EMBASE and The Cochrane Library electronic databases, from inception to 4 July 2019. Variations of the terms 'heart' or 'cardiac' were combined with variants for the terms 'diabetes' and 'fetus'. Full detailed search strategies are presented in Table S1. Retrieved articles were cross-referenced using Web of Science to identify articles missed by the initial search.

Eligibility criteria

Studies were eligible for inclusion if they assessed cardiac function by ultrasound in fetuses of mothers with diabetes, either PDM (type 1 or type 2) or GDM, during pregnancy, compared with fetuses of healthy pregnant women. We included studies performing single or serial ultrasound measurements at any time during pregnancy. Only prenatal cardiac function was reviewed. Language was restricted to English. Reviews, letters to the editor, case reports or case series without a control group were excluded.

Ultrasound measurements

Fetal cardiac function was reviewed in four categories: cardiac hypertrophy, systolic function, diastolic function and overall cardiac function. Although hypertrophy is not strictly a measure of cardiac function, it was included in this review owing to its association with functional cardiac impairment. The ultrasound parameters that were considered per category are summarized in Table 1[18–20].

Study selection

Two reviewers (A.L.D. and L.d.W.) independently screened titles and abstracts and subsequently performed final selection of the eligible studies based on full-text

Table 1 Echocardiographic parameters of fetal cardiac function

Parameter	Type	Assessment
Interventricular septal thickness	Myocardial thickness	Cardiac hypertrophy
Ventricular wall (left and/or right) thickness	Myocardial thickness	Cardiac hypertrophy
Ejection fraction	Blood volume	Systolic function
Fractional shortening	Ventricular diameter	Systolic function
Cardiac output	Blood volume	Systolic function
Isovolumetric contraction time	Time interval	Systolic function
Isovolumetric relaxation time	Time interval	Diastolic function
Flow velocities (E, A, S waves)	Blood flow	Diastolic or systolic function
Tissue velocities (E′, A′, S′ waves, strain, strain rate, peak strain)	Myocardial deformation	Diastolic or systolic function
E/A ratio	Ratio of velocities	Diastolic function
Myocardial performance index*	Ratio of time intervals	Overall function

*Myocardial performance index = (isovolumetric contraction time + isovolumetric relaxation time)/ejection time.

review. Disagreements between the two reviewers were resolved by consensus or by consultation with a third reviewer (M.N.B.) if necessary.

Data extraction

All included studies were reviewed for study design, number of cases and controls, type of diabetes (PDM or GDM), need for pharmacological treatment and glycemic control in diabetic pregnancies, gestational age at the time of the ultrasound examination, ultrasound technique used, parameters measured and resulting outcomes. For each study, the outcome for each of the four categories of fetal cardiac function was classified as increased, decreased or no difference in women with diabetes compared with controls. Additional study characteristics that were extracted were mean maternal body mass index (BMI) and age, timing of GDM diagnosis, duration of PDM and criteria for excluding cases based on pre-existing congenital anomalies.

For the three most widely used ultrasound parameters of fetal cardiac function (interventricular septal (IVS) thickness for myocardial thickness (diastolic), E/A ratio for diastolic function and myocardial performance index (MPI) for overall cardiac function), data were extracted as mean ± SD for meta-analysis where possible.

Risk of bias and quality assessment

The internal validity of the individual studies was assessed using the Newcastle–Ottawa Scale (NOS), following the recommendation of the Cochrane Collaboration for risk of bias analysis in observational studies[21,22]. This scale appraises the selection of cases and controls and comparability and assessment of outcome, including follow-up. The NOS has the possibility of adding study-specific elements to the criteria. In the comparability domain, we chose to assess matching of, or adjustment for, maternal age and BMI. Studies measuring fetal cardiac function at a single timepoint only could not be scored for loss to follow-up. Two reviewers scored the included studies independently, and disagreements were resolved by consensus. No studies were excluded based on the risk

of bias assessment. Publication bias was assessed visually by means of funnel plots[23].

Data reporting and statistical analysis

In addition to reporting the results from individual studies, we also aggregated findings for each category of cardiac function (myocardial thickness, diastolic function, systolic function and overall function) and reported the corresponding outcome (increased, decreased or no difference). This was determined by expressing the absolute number of studies per outcome and the corresponding number of cases per outcome as percentages of the total number of studies and cases in that category, respectively. We further stratified these findings according to type of diabetes (PDM or GDM) and the trimester of pregnancy in which the assessment was performed. We drafted a final conclusion of the combined studies, either increased, decreased or no difference, which was based on the highest count of studies and cases per category. If none of the outcomes was clearly dominant, the overall outcome was scored as inconclusive.

For the meta-analysis, we calculated mean difference between pregnancies complicated by diabetes and controls for IVS thickness, E/A ratio and MPI, using Review Manager version 5.3 (The Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark) with inverse-variance weights. Interstudy heterogeneity was assessed using χ^2 heterogeneity. The I^2 statistic was calculated to assess the proportion of the total variation in study estimates that was due to heterogeneity, and a random-effects model was applied whenever it exceeded 25%[21,23,24]. For the three ultrasound parameters, we performed the analyses according to the type of diabetes (PDM, GDM or mixed/unspecified), stratified by the trimester in which the assessment was performed.

E/A ratio and MPI can be measured in both sides of the fetal heart. If a study performed measurements in both sides of the heart and reported the findings separately, we selected the left-sided measurement for analysis, as these were reported most frequently. Furthermore, for meta-analysis of all three indices, if a study with a mixed population only reported the results separately

for each type of diabetes, we selected either the largest reported group or, in cases of similar-sized groups, we selected the PDM group. If cardiac performance indices were evaluated multiple times per pregnancy, we selected either the outcomes from the largest reported group or, if similar, the measurements obtained closest to 30 weeks' gestation.

RESULTS

Literature search

The search identified a total of 4316 records. After removing duplicates, 3133 records were screened for eligibility. Title and abstract screening resulted in 76 potentially eligible studies. Two studies were identified that respectively reported overall and diastolic cardiac function in the same patient population[25,26]. As both outcome measures were relevant for this review, we included both studies but handled them as a single study. Hence, a total of 39 studies met the inclusion criteria and were included in this review (Figure 1)[11–13,25–61]. Of these, 31 studies reported data on IVS thickness, E/A ratio and/or MPI and were included in the meta-analysis[11,12,25–28,30–36,38,39,41,42,45–53,55–60].

Study characteristics

All 39 studies were observational cohort studies with a control group. Study characteristics are presented in Table S2. Collectively, the studies presented data for 1925 diabetic pregnancies and 2276 controls. Fetal cardiac function was measured in the first trimester (three studies), second trimester (19 studies) and/or third trimester (33 studies). Fifteen studies performed measurements in multiple trimesters. The most commonly used ultrasound methods were M-mode and Doppler, either spectral or pulsed wave. Tissue Doppler imaging was performed in four studies[11,28,30,32]. More recently published studies used velocity vector imaging (VVI)[44,55], or speckle-tracking echocardiography[42,46,48,56]. Of all cases, 1120 had GDM, 671 had PDM and in 134 cases the type of diabetes was not specified. Of the 1925 diabetic women, 862 were on insulin therapy (44.8%), 48 received oral medication (2.5%) and another 34 received insulin and/or oral medication (1.8%). In the remaining women, diabetes treatment was not reported. Glycemic control was defined as good in 16 studies and poor in two studies. Another nine studies included both poorly controlled and well controlled patients, and 12 studies did not describe glycemic control. The definition for glycemic
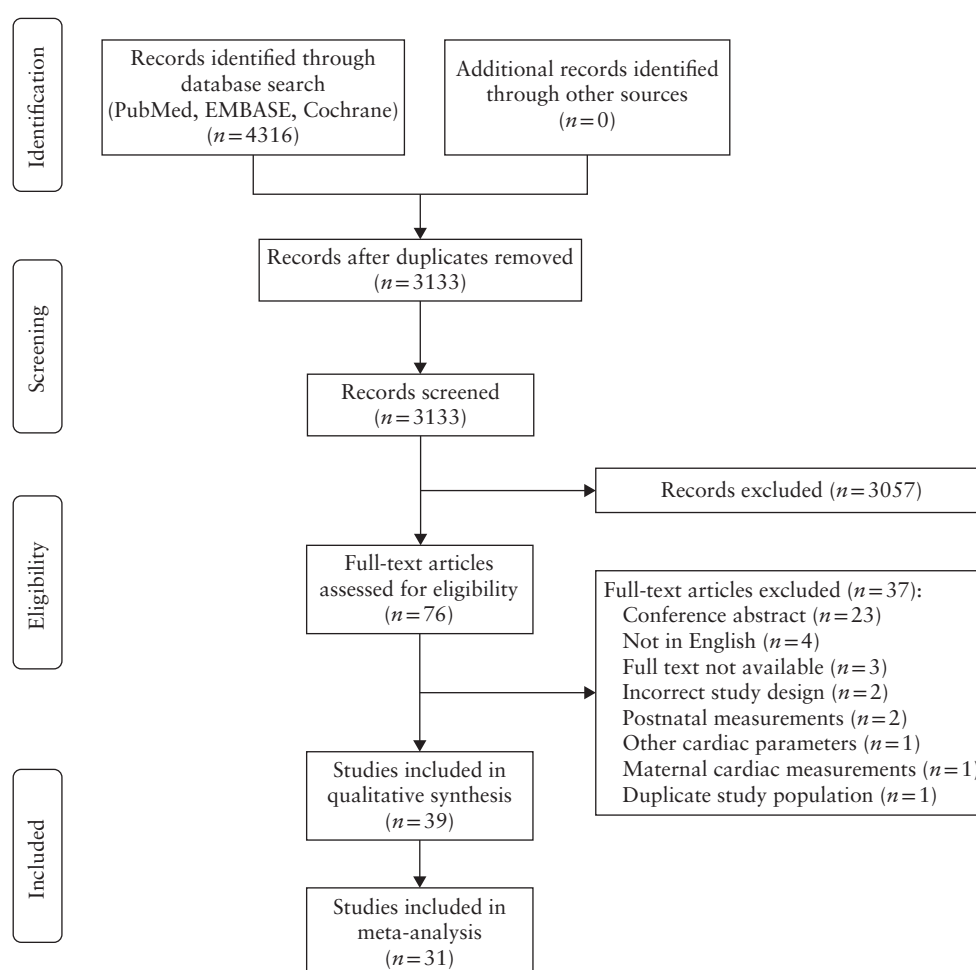

Figure 1 Flowchart summarizing inclusion in systematic review of studies on effect of maternal diabetes on fetal cardiac function.

control varied across studies, but good control was defined most often as glycated hemoglobin values between 5.8% and 6.9%. Additional study characteristics, including maternal parameters, timing of the diagnosis of GDM, duration of PDM and description of exclusion criteria for fetal cardiac structural anomalies are listed in Table S3.

Risk of bias and quality assessment

The majority of studies (32/39 (82.1%)) described the evaluation and exclusion of structural (cardiac) abnormalities prior to assessing fetal cardiac function. The appraisal of included studies by NOS is presented in Table S4. Almost all studies selected a representative cohort with ascertainment of the exposure by a glucose tolerance test (in cases of GDM) and a control group from the same population. However, descriptions of the type of diabetes, severity, duration (for PDM) and diagnostic criteria (for GDM) were often incomplete or missing. Although most studies performed the ultrasound measurements within a similar gestational period in both cases and controls, matching of, or adjustment for, our prespecified factors of maternal age and/or maternal BMI was done in only six studies. Visual inspection of funnel plots for the meta-analysis outcomes suggested no major concerns of publication bias (Figures S1–S3).

Outcomes

The findings of cardiac functional outcome measures and the outcome (increased, decreased or no difference) per category of cardiac function (cardiac hypertrophy, diastolic function, systolic function and overall cardiac function) in each study are presented in Table S2. A summary of the conclusions for each category is shown stratified for the type of diabetes (PDM or GDM) in Table 2 and for the trimester of pregnancy in Table 3. The calculations used to derive the summarized conclusions are provided in Table S5.

Of 26 studies reporting on myocardial thickness, the majority (21 studies) reported significantly thicker IVS or a significantly higher prevalence of cardiac hypertrophy in diabetic pregnancies than in controls. This effect was found in both PDM and GDM pregnancies and was most visible in the third trimester. In 22 of 28 studies reporting on diastolic function, significant impairment was found in diabetic pregnancies, mainly in the first and third trimesters and for both PDM and GDM. Fetal cardiac systolic function was assessed in 25 studies, of which 10 found no significant differences between diabetic pregnancies and controls, with most using fractional shortening to assess systolic function. Six studies measuring ejection fraction or cardiac output found increased systolic function in diabetic pregnancies, whereas decreased systolic function was found in nine studies. Of these, two studies used VVI[44,55] and four used speckle tracking[42,46,48,56]. The majority of studies (14 of 21) reported significantly higher MPI in diabetic pregnancies than in controls. These results, indicative of decreased overall cardiac function, were observed in PDM as well as GDM pregnancies and across all trimesters.

Five of the included studies reported on IVS thickness, E/A ratio and MPI stratified according to the level of glycemic control (Table S6). The results of individual studies suggest thicker IVS in poorly controlled than in well controlled diabetes, and possibly higher MPI. The number of studies and adequate reporting of maternal glycemic control within studies was too limited to perform a meta-analysis for these outcomes.

Meta-analysis

Thirty-one studies reported data on IVS thickness, E/A ratio and/or MPI allowing meta-analysis. The mean (SD) of IVS thickness, E/A ratio and MPI could be extracted from, respectively, 21 studies[12,27,28,31,32,34–36,38,39,41,45,47,48,50,52,55–58,60], 20 studies[11,12,27,28,30–32,34,36,38,41,42,48–53,59,60] and 17

Table 2 Overall conclusion regarding fetal cardiac function in diabetic pregnancies compared with controls, overall and according to type of diabetes

Parameter	All diabetes	PDM	GDM
Myocardial thickness	Increased	Increased	Increased
Diastolic function	Decreased	Decreased	Decreased
Systolic function	Inconclusive	No difference	Inconclusive
Overall cardiac function	Decreased	Decreased	Decreased

GDM, gestational diabetes mellitus; PDM, pregestational diabetes mellitus.

Table 3 Overall conclusion regarding fetal cardiac function in diabetic pregnancies compared to controls, according to trimester in which assessment was performed

Parameter	First trimester	Second trimester	Third trimester
Myocardial thickness	No difference	Increased	Increased
Diastolic function	Decreased	No difference	Decreased
Systolic function	No difference	Inconclusive	Inconclusive
Overall cardiac function	Decreased	No difference	Decreased

studies[12,25,27,28,30,31,33,36,39,42,46–48,50,51,53,60]. Forest plots for each parameter, stratified according to the trimester in which assessment was performed, are presented for PDM and GDM pregnancies separately in Figures 2–4 and for studies with a mixed population or in which the type of diabetes was unspecified in Figures S4–S6. Meta-analysis using a random-effects model showed that IVS thickness in the third trimester was higher in diabetic pregnancies than in controls for both PDM (mean difference, 0.75 mm (95% CI, 0.56–0.94 mm)) and GDM (mean difference, 0.65 mm (95% CI, 0.39–0.91 mm)) (Figure 2). Data for IVS thickness in the second trimester showed significantly higher values in PDM pregnancies than in controls (mean difference, 0.27 mm (95% CI, 0.10–0.43 mm)), but not in GDM pregnancies (mean difference, −0.02 mm (95% CI, −0.21 to 0.17 mm)). The E/A ratio in the third trimester was lower in PDM pregnancies than in controls (mean difference, −0.09 (95% CI, −0.15 to −0.03)) but not in GDM pregnancies (mean difference, −0.01 (95% CI, −0.02 to 0.01)) (Figure 3). Conversely, data from the second trimester indicated significantly lower E/A ratio in GDM pregnancies than in controls (mean difference, −0.04 (95% CI, −0.06 to −0.02)) but not in PDM pregnancies (mean difference, −0.03 (95% CI, −0.07 to 0.02)). MPI in the third trimester was similar in diabetic pregnancies and in controls for both PDM (mean difference, 0.04 (95% CI, −0.01 to 0.09)) and GDM (mean difference, 0.03 (95% CI, −0.01 to 0.06)) (Figure 4). Meta-analysis of studies with a mixed population or unspecified type of diabetes showed no significant difference in IVS, E/A ratio or MPI between diabetic pregnancies and controls in any trimester (Figures S4–S6). The χ-square test and I^2 statistic showed considerable heterogeneity between studies in the analysis of all three parameters.

DISCUSSION

This systematic review provides a comprehensive overview of the effects of maternal diabetes on fetal cardiac function assessed by ultrasound. Compared with non-diabetic controls, fetal cardiac hypertrophy, diastolic dysfunction and overall impaired myocardial performance measures were observed more frequently in women with either PDM or GDM.

The pathophysiology behind the effects of maternal diabetes on the fetal heart is multifactorial and incompletely understood[62]. Structural anomalies may result directly from the hyperglycemic environment, activating a cascade of cellular events and changes in gene expression[63–67]. This may explain why congenital anomalies are more frequent in PDM, in which hyperglycemia is already present during fetal organogenesis, than in GDM. Morphological and hemodynamic changes are more likely to involve abnormal adaptation mechanisms rather than impaired early development. Interestingly, impaired fetal cardiac function was also observed in the majority of studies on GDM, which usually affects maternal glucose levels less severely. Moreover, these changes occurred

even in GDM cases with good glycemic control[27,28,31,51]. Although glycemic control presumably affects the occurrence and extent of myocardial dysfunction, separate analysis was not possible owing to inconsistent or limited reporting of glycemic status.

Morphological fetal cardiac changes have been found to be associated with fetal hyperinsulinemia and insulin-like growth factor-I (IGF-1). IGF-1 promotes hypertrophy in cardiomyocytes, leading to decreased myocardial compliance and functional impairment[9,39,68–71]. Hypertrophy and decreased cardiac function have also been demonstrated in well controlled diabetic pregnancies, suggesting that other factors also play a role[28,31]. The absence of hypertrophy does not exclude functional impairment, and early functional impairment itself has been suggested to induce cardiac hypertrophy[27,50,60]. Congruent with the hyperinsulinemia pathway, fetal macrosomia has been found to be associated with myocardial dysfunction[33]. Further evaluation is needed to determine whether fetal macrosomia is related to fetal cardiac functional changes and could be used as a prognostic factor.

Although maternal age and obesity are associated with impaired fetal cardiac development, matching or correcting for these factors was not often performed in the included studies[9,67,72,73]. In one study, maternal BMI was found not to affect ventricular global longitudinal strain measurements[46], while the results of another study indicated that maternal BMI is a confounding factor in MPI differences between diabetic pregnancies and controls[33]. In the study of Gonzalez *et al.*[39], when matched for BMI, increased IVS thickness was found in the diabetic group compared with controls; however, overall cardiac function did not differ. The extent to which BMI exerts an effect on fetal cardiac development, if any, requires further clarification.

Some studies found changes in fetal cardiac function as early as the first trimester[49,50,53]. Three studies found decreased diastolic and overall function in the first trimester in PDM pregnancies, and multiple studies showed IVS hypertrophy in the second trimester, even in GDM pregnancies[42]. Similarly, significantly increased IVS and decreased MPI and diastolic function in GDM pregnancies at around 24 weeks' gestation has been observed[27]. This indicates that changes in cardiac remodeling can develop at any time during pregnancy. However, with only a few studies performing serial measurements, and given the different patterns of impairment found, the sequence in which they occur is unknown.

Changes in prenatal functional cardiac parameters have been found to be associated directly with adverse neonatal outcome[12,13,29,33,51]. These adverse outcomes have been observed in studies reporting even smaller differences between diabetic pregnancies and controls than we found in our meta-analysis of IVS thickness and E/A ratio. Impaired cardiac function can persist during the first days postpartum and may be accompanied by impaired transitional hemodynamics[15,48,74–77]. The potential benefit of evaluating fetal cardiac function,

(a)

Study or subgroup	PDM pregnancy			Healthy controls			Weight	Mean difference IV, random, 95% CI
	Mean	SD	Total	Mean	SD	Total		
Second trimester								
Gandhi (1995)[35]	2.73	0.57	13	2.23	0.55	6	4.9%	0.50 (−0.04 to 1.04)
Jaeggi (2001)[41]	1.73	0.2	45	1.52	0.3	45	9.7%	0.21 (0.10 to 0.32)
Macklon (1998)[45]	2.1	0.2	10	1.9	0.2	10	9.0%	0.20 (0.02 to 0.38)
Russell (2008)[50]	2.45	0.56	26	2.53	0.56	30	7.6%	−0.08 (−0.37 to 0.21)
Weber (1991)[58]	3.5	0.2	10	3	0.2	19	9.3%	0.50 (0.35 to 0.65)
Weber (1994)[57]	4.5	0.6	9	4.1	0.4	11	5.7%	0.40 (−0.06 to 0.86)
Subtotal (95% CI)			113			121	46.1%	0.27 (0.10 to 0.43)

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 16.97$, df = 5 ($P = 0.005$); $I^2 = 71\%$
Test for overall effect: $Z = 3.19$ ($P = 0.001$)

Third trimester								
Dervisoglu (2018)[32]	4	2.1	32	3.08	1.2	42	2.9%	0.92 (0.11 to 1.73)
Fouda (2013)[34]	4.49	0.93	47	3.63	0.42	32	7.5%	0.86 (0.56 to 1.16)
Gandhi (1995)[35]	4.45	0.17	5	3.85	0.5	5	5.6%	0.60 (0.14 to 1.06)
Gonzalez (2014)[39]	3.8	1.3	55	2.8	0.5	20	6.2%	1.00 (0.59 to 1.41)
Jaeggi (2001)[41]	3.57	0.4	45	2.98	0.39	45	9.2%	0.59 (0.43 to 0.75)
Russell (2008)[50]	5.3	1.27	26	4.63	0.88	30	4.5%	0.67 (0.09 to 1.25)
Tsyvian (1998)[52]	3.2	0.4	15	2.8	0.5	25	7.8%	0.40 (0.12 to 0.68)
Weber (1991)[58]	5.3	0.5	9	4	0.3	6	6.3%	1.30 (0.89 to 1.71)
Weber (1994)[57]	5.3	0.7	9	4.7	0.8	11	3.9%	0.60 (−0.06 to 1.26)
Subtotal (95% CI)			243			216	53.9%	0.75 (0.56 to 0.94)

Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 18.17$, df = 8 ($P = 0.02$); $I^2 = 56\%$
Test for overall effect: $Z = 7.66$ ($P < 0.00001$)

Total (95% CI)			356			337	100.0%	0.53 (0.37 to 0.70)

Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 74.29$, df = 14 ($P < 0.00001$); $I^2 = 81\%$
Test for overall effect: $Z = 6.32$ ($P < 0.00001$)
Test for subgroup differences: $Chi^2 = 13.94$, df = 1 ($P = 0.0002$), $I^2 = 92.8\%$

Decreased IVS   Increased IVS

(b)

Study or subgroup	GDM pregnancy			Healthy controls			Weight	Mean difference IV, random, 95% CI
	Mean	SD	Total	Mean	SD	Total		
Second trimester								
Atiq (2017)[27]	2.1	0.4	64	2.2	0.3	64	8.7%	−0.10 (−0.22 to 0.02)
Wong (2007)[60]	2.1	0.5	32	2	0.5	44	8.4%	0.10 (−0.13 to 0.33)
Subtotal (95% CI)			96			108	17.1%	−0.02 (−0.21 to 0.17)

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 2.30$, df = 1 ($P = 0.13$); $I^2 = 56\%$
Test for overall effect: $Z = 0.25$ ($P = 0.80$)

Third trimester								
Balli (2014)[28]	3.76	0.48	67	3.07	0.27	122	8.7%	0.69 (0.57 to 0.81)
Chu (2012)[31]	3.9	0.6	19	3	0.5	20	7.9%	0.90 (0.55 to 1.25)
Dervisoglu (2018)[32]	3.2	0.1	36	3.08	1.2	42	7.8%	0.12 (−0.24 to 0.48)
Fouda (2013)[34]	4.01	0.78	40	3.63	0.42	32	8.2%	0.38 (0.10 to 0.66)
Garcia-Flores (2011)[36]	3.93	0.57	24	3.05	0.23	16	8.3%	0.88 (0.63 to 1.13)
Garg (2014)[38]	3.74	0.98	276	2.77	0.86	294	8.7%	0.97 (0.82 to 1.12)
Moghadam (2019)[47]	2.3	0.7	25	2	0.04	50	8.2%	0.30 (0.03 to 0.57)
Wang (2015)[56]	3.16	0.51	35	2.88	0.48	60	8.5%	0.28 (0.07 to 0.49)
Wang (2016)[55]	4.75	0.89	87	3.19	0.53	120	8.5%	1.56 (1.35 to 1.77)
Wong (2007)[60]	2.8	0.7	35	2.5	0.7	42	8.1%	0.30 (−0.01 to 0.61)
Subtotal (95% CI)			644			798	82.9%	0.65 (0.39 to 0.91)

Heterogeneity: $Tau^2 = 0.16$; $Chi^2 = 123.70$, df = 9 ($P < 0.00001$); $I^2 = 93\%$
Test for overall effect: $Z = 4.84$ ($P < 0.00001$)

Total (95% CI)			740			906	100.0%	0.54 (0.24 to 0.83)

Heterogeneity: $Tau^2 = 0.26$; $Chi^2 = 274.19$, df = 11 ($P < 0.00001$); $I^2 = 96\%$
Test for overall effect: $Z = 3.53$ ($P = 0.0004$)
Test for subgroup differences: $Chi^2 = 16.52$, df = 1 ($P < 0.0001$), $I^2 = 93.9\%$
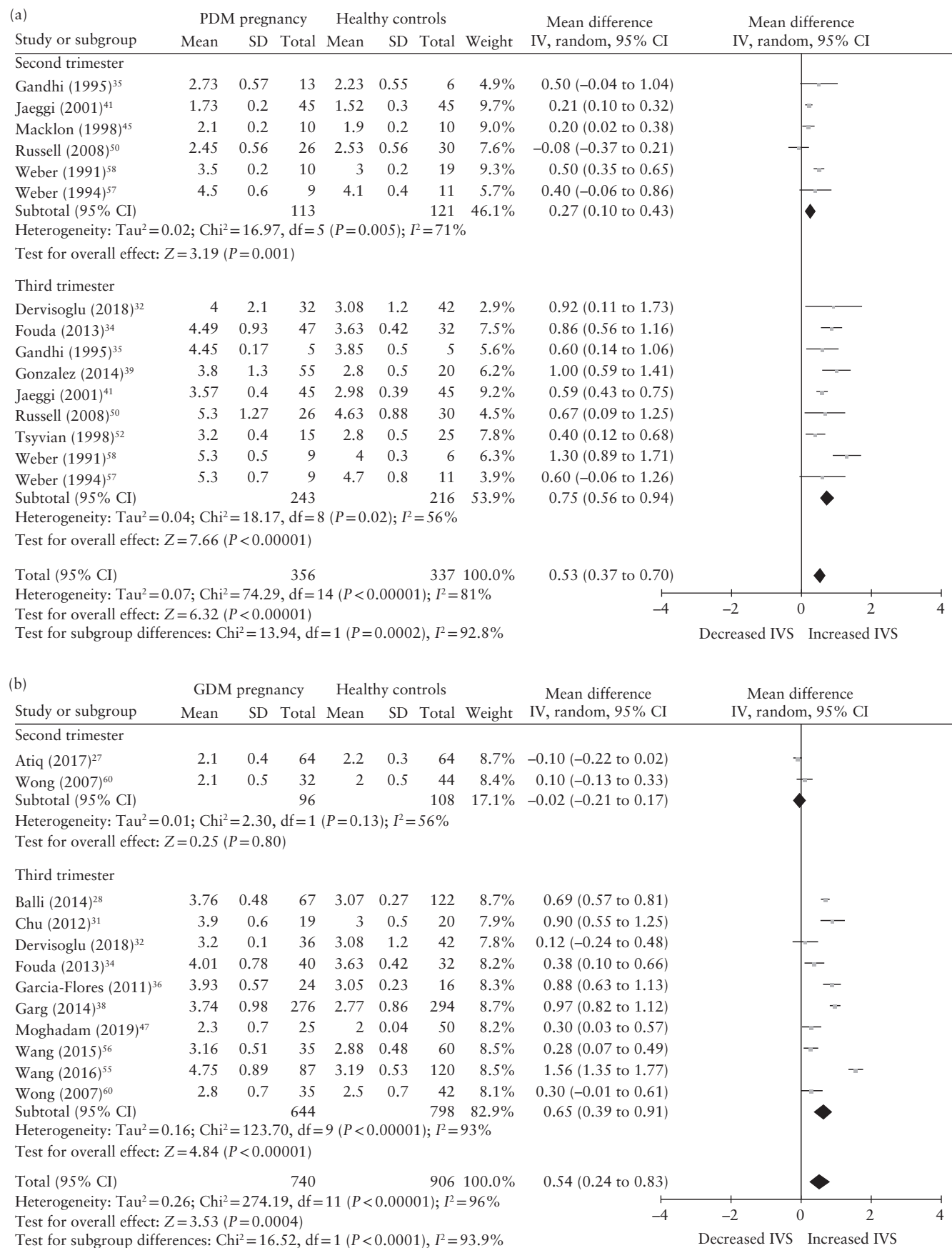
Decreased IVS   Increased IVS

Figure 2 Forest plots of difference in fetal interventricular septal thickness (IVS) (mm) between pregnancies with pregestational diabetes mellitus (PDM) (10 studies) (a) or gestational diabetes mellitus (GDM) (11 studies) (b) and controls, according to trimester in which assessment was performed. IV, inverse variance.
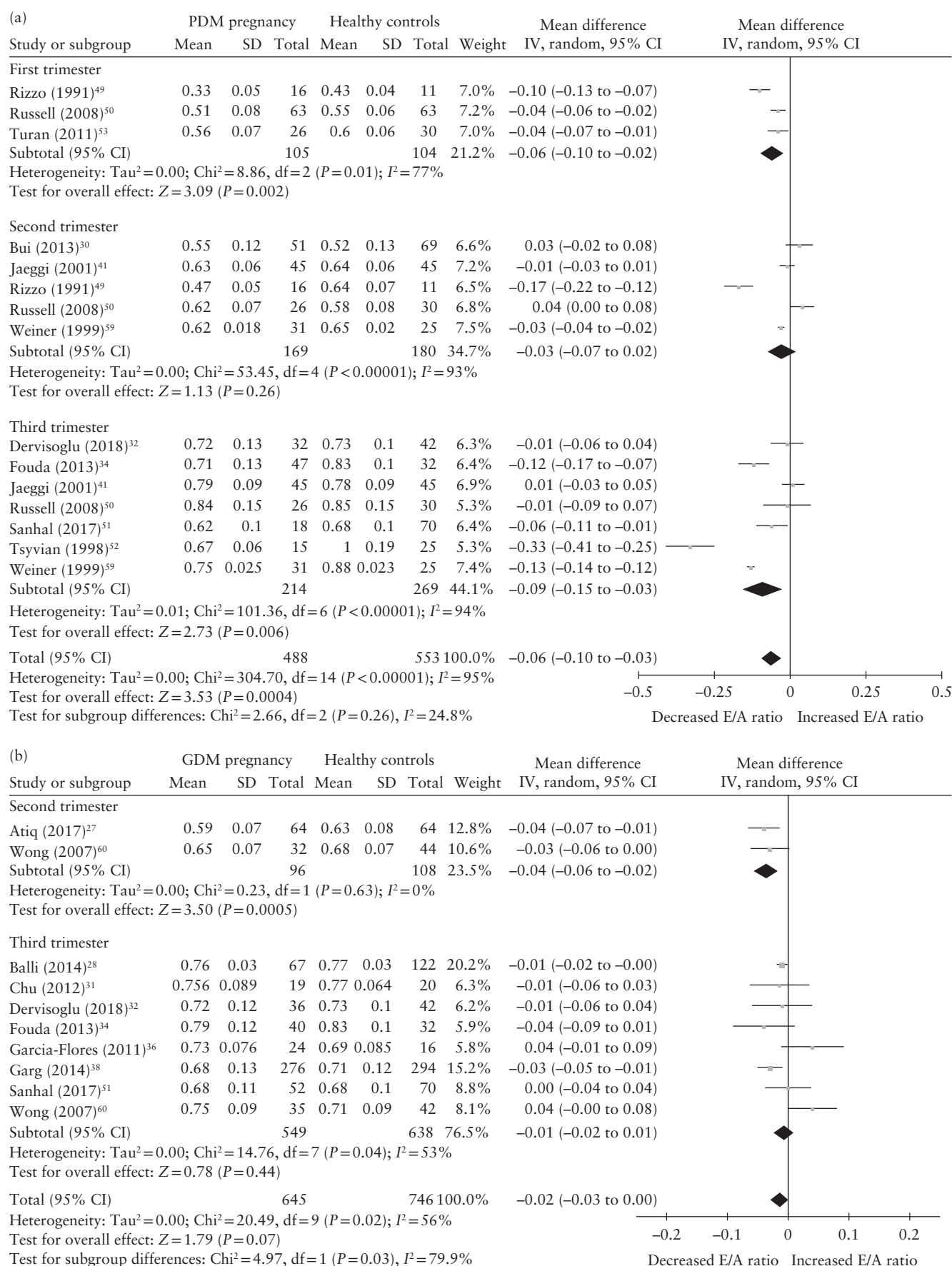
(a)

Study or subgroup	PDM pregnancy			Healthy controls			Weight	Mean difference IV, random, 95% CI
	Mean	SD	Total	Mean	SD	Total		
First trimester								
Rizzo (1991)[49]	0.33	0.05	16	0.43	0.04	11	7.0%	−0.10 (−0.13 to −0.07)
Russell (2008)[50]	0.51	0.08	63	0.55	0.06	63	7.2%	−0.04 (−0.06 to −0.02)
Turan (2011)[53]	0.56	0.07	26	0.6	0.06	30	7.0%	−0.04 (−0.07 to −0.01)
Subtotal (95% CI)			105			104	21.2%	−0.06 (−0.10 to −0.02)

Heterogeneity: Tau² = 0.00; Chi² = 8.86, df = 2 (P = 0.01); I² = 77%
Test for overall effect: Z = 3.09 (P = 0.002)

Second trimester								
Bui (2013)[30]	0.55	0.12	51	0.52	0.13	69	6.6%	0.03 (−0.02 to 0.08)
Jaeggi (2001)[41]	0.63	0.06	45	0.64	0.06	45	7.2%	−0.01 (−0.03 to 0.01)
Rizzo (1991)[49]	0.47	0.05	16	0.64	0.07	11	6.5%	−0.17 (−0.22 to −0.12)
Russell (2008)[50]	0.62	0.07	26	0.58	0.08	30	6.8%	0.04 (0.00 to 0.08)
Weiner (1999)[59]	0.62	0.018	31	0.65	0.02	25	7.5%	−0.03 (−0.04 to −0.02)
Subtotal (95% CI)			169			180	34.7%	−0.03 (−0.07 to 0.02)

Heterogeneity: Tau² = 0.00; Chi² = 53.45, df = 4 (P < 0.00001); I² = 93%
Test for overall effect: Z = 1.13 (P = 0.26)

Third trimester								
Dervisoglu (2018)[32]	0.72	0.13	32	0.73	0.1	42	6.3%	−0.01 (−0.06 to 0.04)
Fouda (2013)[34]	0.71	0.13	47	0.83	0.1	32	6.4%	−0.12 (−0.17 to −0.07)
Jaeggi (2001)[41]	0.79	0.09	45	0.78	0.09	45	6.9%	0.01 (−0.03 to 0.05)
Russell (2008)[50]	0.84	0.15	26	0.85	0.15	30	5.3%	−0.01 (−0.09 to 0.07)
Sanhal (2017)[51]	0.62	0.1	18	0.68	0.1	70	6.4%	−0.06 (−0.11 to −0.01)
Tsyvian (1998)[52]	0.67	0.06	15	1	0.19	25	5.3%	−0.33 (−0.41 to −0.25)
Weiner (1999)[59]	0.75	0.025	31	0.88	0.023	25	7.4%	−0.13 (−0.14 to −0.12)
Subtotal (95% CI)			214			269	44.1%	−0.09 (−0.15 to −0.03)

Heterogeneity: Tau² = 0.01; Chi² = 101.36, df = 6 (P < 0.00001); I² = 94%
Test for overall effect: Z = 2.73 (P = 0.006)

Total (95% CI)			488			553	100.0%	−0.06 (−0.10 to −0.03)

Heterogeneity: Tau² = 0.00; Chi² = 304.70, df = 14 (P < 0.00001); I² = 95%
Test for overall effect: Z = 3.53 (P = 0.0004)
Test for subgroup differences: Chi² = 2.66, df = 2 (P = 0.26), I² = 24.8%

Decreased E/A ratio   Increased E/A ratio

(b)

Study or subgroup	GDM pregnancy			Healthy controls			Weight	Mean difference IV, random, 95% CI
	Mean	SD	Total	Mean	SD	Total		
Second trimester								
Atiq (2017)[27]	0.59	0.07	64	0.63	0.08	64	12.8%	−0.04 (−0.07 to −0.01)
Wong (2007)[60]	0.65	0.07	32	0.68	0.07	44	10.6%	−0.03 (−0.06 to 0.00)
Subtotal (95% CI)			96			108	23.5%	−0.04 (−0.06 to −0.02)

Heterogeneity: Tau² = 0.00; Chi² = 0.23, df = 1 (P = 0.63); I² = 0%
Test for overall effect: Z = 3.50 (P = 0.0005)

Third trimester								
Balli (2014)[28]	0.76	0.03	67	0.77	0.03	122	20.2%	−0.01 (−0.02 to −0.00)
Chu (2012)[31]	0.756	0.089	19	0.77	0.064	20	6.3%	−0.01 (−0.06 to 0.03)
Dervisoglu (2018)[32]	0.72	0.12	36	0.73	0.1	42	6.2%	−0.01 (−0.06 to 0.04)
Fouda (2013)[34]	0.79	0.12	40	0.83	0.1	32	5.9%	−0.04 (−0.09 to 0.01)
Garcia-Flores (2011)[36]	0.73	0.076	24	0.69	0.085	16	5.8%	0.04 (−0.01 to 0.09)
Garg (2014)[38]	0.68	0.13	276	0.71	0.12	294	15.2%	−0.03 (−0.05 to −0.01)
Sanhal (2017)[51]	0.68	0.11	52	0.68	0.1	70	8.8%	0.00 (−0.04 to 0.04)
Wong (2007)[60]	0.75	0.09	35	0.71	0.09	42	8.1%	0.04 (−0.00 to 0.08)
Subtotal (95% CI)			549			638	76.5%	−0.01 (−0.02 to 0.01)

Heterogeneity: Tau² = 0.00; Chi² = 14.76, df = 7 (P = 0.04); I² = 53%
Test for overall effect: Z = 0.78 (P = 0.44)

Total (95% CI)			645			746	100.0%	−0.02 (−0.03 to 0.00)

Heterogeneity: Tau² = 0.00; Chi² = 20.49, df = 9 (P = 0.02); I² = 56%
Test for overall effect: Z = 1.79 (P = 0.07)
Test for subgroup differences: Chi² = 4.97, df = 1 (P = 0.03), I² = 79.9%

Decreased E/A ratio   Increased E/A ratio

Figure 3 Forest plots of difference in fetal E/A ratio between pregnancies with pregestational diabetes mellitus (PDM) (10 studies) (a) or gestational diabetes mellitus (GDM) (9 studies) (b) and controls, according to trimester in which assessment was performed. IV, inverse variance.

however, may lie in its prognostic value for long-term (cardiac) health. Research in animals has shown that diabetes, especially when combined with a high-fat diet, impairs cardiac function in the offspring, and cardiometabolic gene evaluations suggest the occurrence of fuel-mediated epigenetic reprogramming of cardiac tissue *in utero*[78]. Affected genes are involved in metabolic processes related to blood pressure, body weight, cholesterol level and susceptibility to cardiac disease. Although maternal diabetes is clearly associated with an increased risk for cardiovascular disease in human offspring[79–83], studies directly evaluating fetal cardiac health in relation to these long-term outcomes are lacking. Postnatal evaluation in neonates of diabetic mothers has
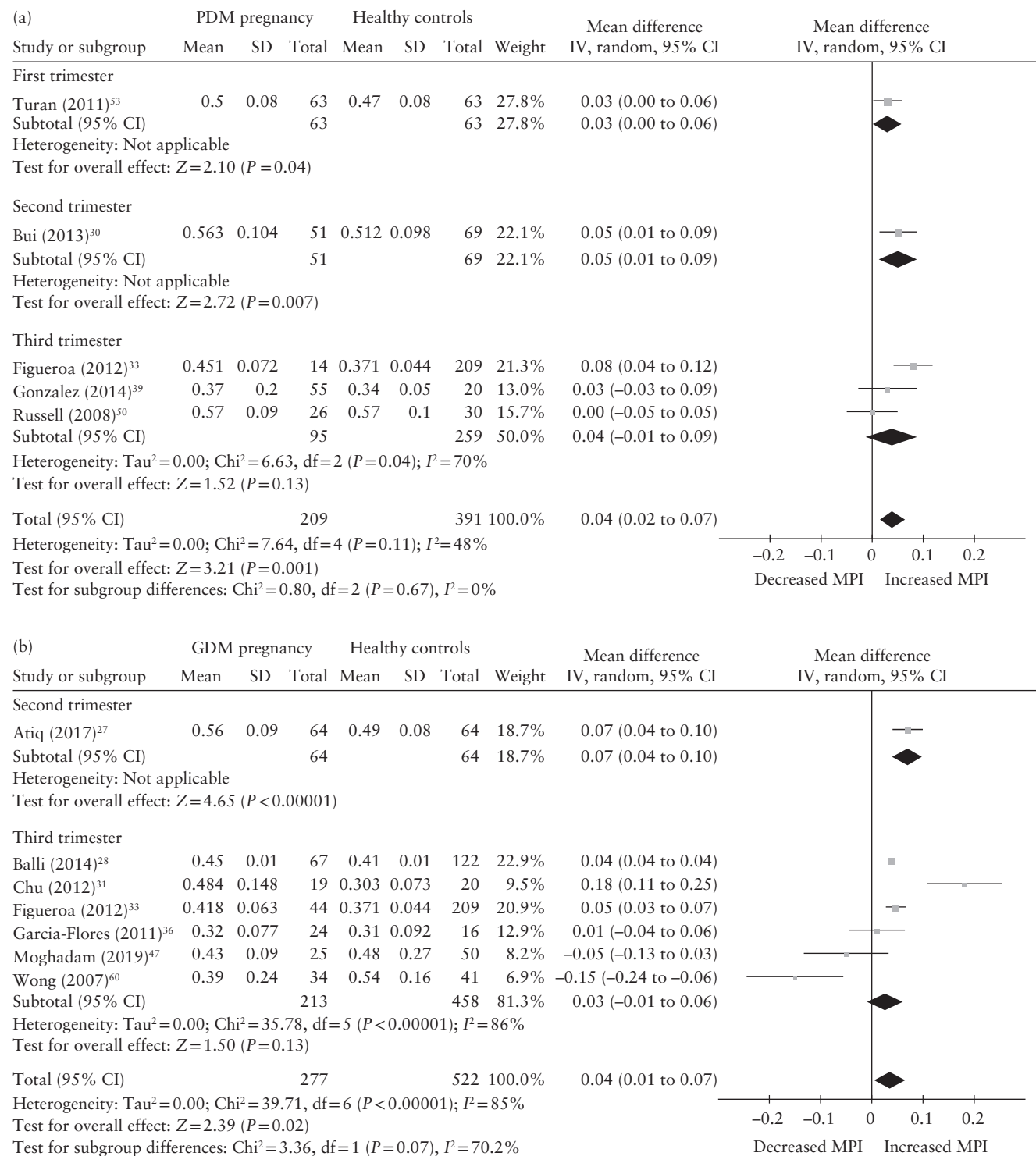
Figure 4 Forest plots of difference in fetal myocardial performance index (MPI) between pregnancies with pregestational diabetes mellitus (PDM) (five studies) (a) or gestational diabetes mellitus (GDM) (seven studies) (b) and controls, according to trimester in which assessment was performed. IV, inverse variance.

shown cardiac hypertrophy to be present in 25–40% of neonates[68,84–88]. Initial sonographic follow-up studies are reassuring, as hypertrophy appears to resolve within the first year postpartum[68,84,85]. However, septal hypertrophy is associated with a large-for-gestational-age infant and increased glycated hemoglobin levels in umbilical cord blood at birth, both of which are associated with metabolic syndrome at a later age[34,79]. Similarly, increased maternal lipid and glucose indices have been linked to decreased ventricular function after birth[14]. Although this has not yet been demonstrated, these findings are suggestive of a correlation between *in-utero* cardiac development and future cardiovascular health. Evaluation of which ultrasound parameters correspond to relevant clinical outcomes is needed.

Our study complements a previous review on fetal cardiac function assessed by ultrasound in PDM pregnancies[9]. In that review, deformation parameters were identified as interesting new alternatives for assessing fetal cardiac function, confirmed by more recent studies included in our review. Cardiac strain-based parameters may have a higher sensitivity for detecting early diastolic dysfunction than do conventional markers. Furthermore, we extended our search and analyses to also include studies on GDM, in addition to PDM. In another review, the E/A ratio and MPI were assessed in PDM and GDM pregnancies, similarly concluding that functional changes exist in affected compared with uncomplicated pregnancies[89].

Limitations common to any systematic review are heterogeneity between studies due to varying definitions, diagnostic criteria, endpoints, clinical treatment, strategies for matching cases and controls and adjustment for potential confounders. An obvious confounder in many reports is maternal BMI which, in addition to maternal age and fetal macrosomia, may be driving some of the observed associations.

In conclusion, we have demonstrated a strong association between maternal diabetes and impaired fetal cardiac function assessed by ultrasound, occurring in both PDM and GDM. Functional changes may occur in the absence of cardiac hypertrophy and in pregnancies with good glycemic control. Studies directly demonstrating the relationship between fetal cardiac dysfunction on ultrasound and future cardiovascular health are lacking. Our findings strongly support the need for further longitudinal studies aimed at demonstrating the plausible association between maternal diabetes and fetal cardiac function *in utero*, in relation to clinical outcomes and offspring development.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Figure S1 Funnel plot for comparison of interventricular septal thickness between pregnancies with diabetes and controls (21 studies).

Figure S2 Funnel plot for comparison of E/A ratio between pregnancies with diabetes and controls (20 studies).

Figure S3 Funnel plot for comparison of myocardial performance index between pregnancies with diabetes and controls (17 studies).

Figure S4 Forest plot of difference in interventricular septal thickness between pregnancies with diabetes and controls, in studies with mixed population or unspecified diabetes type (2 studies).

Figure S5 Forest plot of difference in E/A ratio between pregnancies with diabetes and controls, in studies with mixed population or unspecified diabetes type (4 studies).

Figure S6 Forest plot of difference in myocardial performance index between pregnancies with diabetes and controls, in studies with mixed population or unspecified diabetes type (6 studies).

Table S1 Search strategy for PubMed, EMBASE and Cochrane databases

Table S2 Characteristics, results of fetal cardiac evaluation and conclusion for each category in studies on fetal cardiac function in pregnancies complicated by diabetes

Table S3 Additional characteristics of studies on fetal cardiac function in pregnancies complicated by diabetes

Table S4 Results of Newcastle–Ottawa Quality Assessment Scale (NOS)

Table S5 Summary of number of studies and cases reporting increased, decreased or no difference in fetal cardiac function indices in pregnancies complicated by diabetes compared with controls, overall and according to type of diabetes or trimester in which assessment was performed

Table S6 Fetal interventricular septal thickness, E/A ratio and myocardial performance index in pregnancies with diabetes, according to whether glycemic control was good or poor